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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 10/699,281
Filing Date: October 30, 2003
Appellant(s): WOLBER ET AL.

Bret Field
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 15 June 2007 appealing from the Office action mailed 22 December 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. As noted in the Advisory Action of 7 March 2007, claims 21-25 stand rejected under 35 USC 103(a) and being unpatentable over McGall (U.S. Patent No. 5,843,655, issued 1 December 1998) in view of Weng et al (U.S. Patent No. 6,691,042, issued 10 February 2004).

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,843,655	McGall	12-1998
6,691,042	Weng et al	2-2004

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

Claims 1-13 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over by McGall (U.S. Patent No. 5,843,655, issued 1 December 1998) in view of Weng et al (U.S. Patent No 6,691,042 B2, issued 10 February 2004).

Regarding claim 1, McGall teaches a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, said method comprising contacting an in situ produced nucleic acid array, said array including at least one depurination probe feature having a depurination probe with a sample suspected of having said analyte; namely, McGall teaches a nucleic acid array produced photolithographically (i.e., in situ) and having oligonucleotides thereon (Figure 8), wherein R1 and R2 are the depurination features. R1 and R2 each have a depurination probe; namely, those oligonucleotides marked with a "D" are depurination probes in the feature (column 9, lines 22-38).

McGall teaches that the two areas of the array are exposed to a test condition to test for depurination at the depurination sites D (Figure 8 and column 9, lines 39-49). McGall also teaches that the test condition is followed by exposure to conditions that cleave depurinated sites (column 9, lines 50-60) and subsequent detection of the remaining label from the uncleaved oligonucleotides of the array (column 9, lines 61-67). The detection of the remaining uncleaved oligonucleotides determines the presence of depurination reaction products on the array by comparison of the first cleaved area to the other (i.e., second) area of the array, which is subjected to the same test conditions but not the cleavage

conditions (column 9, lines 61-67); thus, the second area retains all of the oligonucleotides originally present, whereas the cleaved area has lost all of the depurinated oligonucleotides.

While McGall also teaches subjecting the arrays to test conditions, wherein test conditions include operating conditions (column 11, lines 20-41), and wherein operating conditions of the array includes hybridization of nucleic acids to the array (column 13, lines 33-57), McGall does not explicitly show hybridization as a test condition for determining depurination.

However, Weng et al teach a method of detecting the presence of nucleic acids; namely, measuring expression levels of nucleic acids using microarrays (column 8, lines 60-67). Weng et al also teach hybridization is used as a test condition (column 4, lines 58-67), and that hybridization as a test condition has the added benefit of providing a method of controlling the quality of the microarray production process (column 5, lines 29-32).

Use of the hybridization test condition of Weng et al in the method of McGall is thus interpreted as outlined in the single exemplary embodiment: two ensembles of oligonucleotides in two areas of an array of McGall are both subjected to the same hybridization test condition of Weng et al. The ensemble in the first area is subjected to cleavage of depurination products. The amount of label at each site is detected and compared to determine the presence of depurination reaction products on the surface of the array. Thus, the resultant binding complexes of the uncleaved depurination probes with the target nucleic acid are compared to the cleaved binding complexes of the depurination probes with the target nucleic acid to determine the presence of depurination reaction products on the surface of the array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the depurination detection test conditions as taught by McGall using hybridization as a test condition as taught by Weng et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in providing a method of controlling the quality of the microarray production process as explicitly taught by Weng et al (column 5, lines 29-32).

Regarding claim 2, the method of claim 1 is discussed above. McGall also teaches that the method detects the amount of depurination products on said surface; namely, the amount of label in an area is determined after cleavage of the depurinated oligonucleotides (column 2, lines 48-50).

Regarding claim 3, the method of claim 2 is discussed above. McGall also teaches the detection of a relative amount (column 7, lines 63-67).

Regarding claim 4, the method of claim 2 is discussed above. McGall also teaches the labeling of the target nucleic acid (column 11, lines 55-56).

Regarding claim 5, the method of claim 4 is discussed above. McGall also teaches fluorescent labels and signals (column 3, lines 24-31).

Regarding claim 6, the method of claim 5 is discussed above. McGall also teaches a fluorescent signal having an intensity inversely proportional to the amount of depurination products present (column 9, lines 65-67).

Regarding claim 7, the method of claim 1 is discussed above. McGall also teaches an array including two or more different depurination probe features each corresponding to a distinct depurination probe; namely, the array has a plurality of areas R1 and R2 (Figure 8), each having depurinated nucleic acids thereon.

Regarding claim 8, the method of claim 1 is discussed above. McGall also teaches early and late depurination probe features; namely, the depurination features occur at positions in the sequence relative to the surface (Figures 8 and 9).

Regarding claim 9, the method of claim 1 is discussed above. McGall also teaches arrays including two or more features whose synthesis was started at different times; namely, areas on the surface are sequentially synthesized (column 9, lines 30-35).

Regarding claim 10, the method of claim 1 is discussed above. McGall also teaches a known deblock dose; namely, selective deprotection and coupling cycles are repeated until the desired products are obtained (column 5, lines 2-25), the desired products requiring a known number of cycles.

Regarding claim 11, the method of claim 1 is discussed above. McGall also teaches the method further comprises evaluating the level of depurination that occurred during in situ fabrication of said array (column 2, lines 48-50).

Regarding claim 12, the method of claim 11 is discussed above. McGall also teaches the method is a method of evaluating the quality of an in situ nucleic acid array synthesis protocol (column 1, lines 7-9).

Regarding claim 13, the method of claim 12 is discussed above. McGall also teaches the method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to said protocol; namely, arrays in different test areas on the substrate are independently evaluated (column 9, lines 38-49).

Regarding claim 21, McGall teaches a method of detecting the presence of a nucleic acid analyte in a sample, said method comprising contacting a nucleic acid array, said array comprising a set of two or more nucleic acid depurination features each having a depurination probe and having a nucleic acid ligand that specifically binds to said nucleic acid analyte with a sample suspected of having said analyte; namely, McGall teaches Figure 8, which shows regions R1 and R2, which are interpreted as two different features of the array. The instant specification teaches embodiments wherein target molecules are bound to "features or spots (page 1, lines 25-27)," that an array "may contain multiple spots or features (page 7, lines 27-30)," and that a region of the array is either a "feature" or a "spot (page 98, lines 10-12)." Thus, the specification teaches embodiments wherein the "feature" is an alternative to a "spot" because each of the cited recitation refers to features **or** spots, and thus teaches features are not necessarily spots. Thus, the claims have been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "feature" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

McGall further teaches R1 and R2 each have a depurination probe and a nucleic acid ligand; namely, those oligonucleotides marked with a "D" are depurination probes. Lines 5-14 of page 16 of the instant specification states that "depurination probes are probes that have a known number of purine

bases, and specifically Adenosine or A bases." Thus, the broadly claimed "depurination probe" encompasses **any** nucleic acid wherein the number of purine bases, regardless of whether or not any purine of the nucleic acid has been lost.

The specification further teaches that the invention is related to the determination of the extent of depurination in a given lot of nucleic acid arrays produced using an in situ fabrication protocol (page 5, lines 25-30). Thus, even though the broadly claimed "depurination probe" encompasses **any** nucleic acid wherein the number of purine bases, regardless of whether or not any purine of the nucleic acid has been lost, the "depurination probe" of the instant claims is more narrowly interpreted in light of the alternate embodiment as a probe that has actually lost some purines. Thus, the claims have been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "depurination probe" because the probe has actually lost at least one purine as outlined above.

The remaining oligonucleotides are nucleic acid ligands (column 9, lines 22-38) because nucleic acids are first members of binding pairs. Lines 29-35 on page 38 of the instant specification describe an embodiment wherein a ligand is a "first member or a binding pair," which encompasses the nucleic acids immobilized on the array of McGall. Thus, the claims have been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "ligand."

It is noted that the claims examined in the Final Rejection merely required the detection of "binding complexes" on the surface of the array to detect the presence of a nucleic acid analyte; Appellant's after final amendment changes the scope of the claims such that the detected "binding complexes" must be the complexes formed between the nucleic acid ligand and the analyte. Thus, the broadly claimed "binding complexes" encompassed **any** "binding complexes" on the surface of the array and were **not** required to be the **specific** complexes formed by hybridization of the analyte to either the nucleic acid ligands or the depurination probes.

McGall teaches the array is treated with a sample of suspected of comprising said nucleic acid analyte under conditions for binding of said analyte to said nucleic acid ligand on said array to occur;

namely, that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)," wherein the labeled target is the instantly claimed nucleic acid analyte and the oligonucleotide in the array is the instantly claimed nucleic acid ligand. McGall also teaches detecting the presence of binding complexes on the surface of said array to detect the presence of said nucleic acid analyte in said sample; namely, a CCD imaging system is used to detect hybridization (column 13, lines 33-52).

McGall also teaches subjecting the arrays to one or more test conditions, wherein test conditions include operating conditions (column 11, lines 20-41), and wherein operating conditions of the array includes hybridization of nucleic acids to the array (column 13, lines 33-57). Thus, while McGall testing the array to detect depurination (i.e., as a test condition; column 9, lines 22-65), that more than one test condition is applied (column 11, lines 20-41), that test conditions include operating conditions (column 11, lines 20-41), and wherein operating conditions of the array includes hybridization of nucleic acids to the array (column 13, lines 33-57), McGall does not explicitly show hybridization as a test condition for determining depurination.

However, Weng et al teach a method of detecting the presence of nucleic acids; namely, measuring expression levels of nucleic acids using microarrays (column 8, lines 60-67). Weng et al also teach hybridization is used as a test condition (column 4, lines 58-67), and that hybridization as a test condition has the added benefit of providing a method of controlling the quality of the microarray production process (column 5, lines 29-32).

Use of the hybridization test condition of Weng et al in the method of McGall is thus interpreted as outlined in the single exemplary embodiment: two ensembles of oligonucleotides in two areas of an array of McGall are both subjected to the same hybridization test condition of Weng et al. The ensemble in the first area is subjected to cleavage of depurination products. The amount of label at each site is detected and compared to determine the presence of depurination reaction products on the surface of the array. Thus, the resultant binding complexes of the uncleaved depurination probes with the target

nucleic acid are compared to the cleaved binding complexes of the depurination probes with the target nucleic acid to determine the presence of depurination reaction products on the surface of the array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the depurination detection test conditions as taught by McGall using hybridization as a test condition as taught by Weng et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in providing a method of controlling the quality of the microarray production process as explicitly taught by Weng et al (column 5, lines 29-32).

Regarding claim 22, the method of claim 21 is discussed above. McGall also teaches said sample comprises a collection of labeled target nucleic acids that specifically bind to said nucleic acid depurination features (column 13, lines 33-52).

Regarding claim 23, the method of claim 21 is discussed above. McGall also teaches transmitting a result from a reading of an array according to the method of claim 21 from a first location (e.g., the surface of the array) to a second location (e.g., a line scanner; column 12, lines 56-67).

Regarding claim 24, the method of claim 23 is discussed above. McGall also teaches the second location is a remote location; namely, a line scanner (column 12, lines 56-67), which is remote from the surface of the array.

Regarding claim 25, the method of claim 21 is discussed above. McGall also teaches receiving a transmitted result of a reading of an array obtained from the method of claim 21; namely, the transmitted images are stored in a computer (column 12, lines 56-67).

It is noted that the rejections of claims 21-25 of are not new rejections. Claims 21-25 were previously rejected under 35 USC 102(b) in the Final Office Action mailed 22 December 2006. However, as noted in the Advisory Action mailed 7 March 2007, the entering of the after final amendments to independent claim 21 would result in rejection of claims 21-25 under 35 USC 103(a). Thus, the rejections

of claim 21-25 under 35 USC 103(a) are not new rejections, but are rejections of record reiterated above following the rejections of claims 1-13.

(10) Response to Argument

Appellant states on pages 6-7 of the Appeal Brief filed 15 June 2007 (i.e., the "Brief") that the rejected claims will be argued in groups as follows:

Group I, claims 1-7 and 10-12;

Group II, claim 8;

Group III, claim 9;

Group IV, claim 13;

Group V, claims 21 and 23-25; and

Group VI; claim 22.

The examiner's response to Appellant's arguments is presented based on the order of Groups I-VI as presented by Appellant in the Brief.

It is noted that Appellant's arguments on pages 7-13 of the Brief regarding Group V, claims 21 and 23-25, and Group VI, claim 22, refer the previous rejections of the claims as anticipated by McGall under 35 USC 102(b) (Final Action mailed 22 December 2006). However, as noted in section 10, the current rejections of Groups V, claims 21 and 23-25, and Group VI, claim 22, are under 35 USC 103(a) as obvious over McGall in view of Weng et al, which were presented in the Advisory Action mailed 7 March 2007.

Group V, claims 21 and 23-25

Appellant asserts on pages 8-9 of the Brief that the examiner has mischaracterized the art and that McGall does not anticipate contacting the substrate with a sample suspected of containing an analyte.

Contrary to Appellant's assertion, McGall clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13,

lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. In addition, Appellant's arguments regarding anticipation of the claims are irrelevant since the basis for rejections of the claims is obviousness over the teachings of McGall in view of Weng et al rather anticipation of the claims by McGall.

Appellant further argues on page 9 of the Appeal Brief that the test conditions of McGall that lead to removal of depurinated oligonucleotides and determination of the amount of depurination are merely a test condition.

Appellant therefore agrees that the removal of depurination oligonucleotides and determination of the amount of depurination are test conditions according to McGall. As noted in the rejection, the hybridization to a target and the depurination are both interpreted as test conditions and Weng et al provides the motivation for using hybridization as one of the one or more test conditions taught by McGall. Therefore, the claims are obvious over the teachings of McGall in view of Weng et al for the reasons set forth in the rejections above.

Appellant also argues on pages 9-10 of the Brief that McGall does not involve contacting the substrate with a sample suspected of including an analyte.

Contrary to Appellant's argument, McGall clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate with a sample suspected of containing an analyte (i.e., a labeled target oligonucleotide) and detecting the presence of binding complexes on the surface of the array.

Appellant further argues on pages 10-11 of the Brief that McGall establishes no relationship between the "target nucleic acids" of column 13 and the "Rates of Depurination" technique cited for the depurination steps.

Appellant's arguments are irrelevant since the basis for rejections of the claims is obviousness over the teachings of McGall in view of Weng et al rather anticipation. The hybridization to a target and the depurination are both interpreted as test conditions and Weng et al provides the motivation for using hybridization as one of the one or more test conditions taught by McGall.

Appellant also asserts on page 10 of the Brief that McGall does not teach hybridization to targets has an on- or off-rate.

Contrary to Appellant's assertion, McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array is to obtain results of the assay by examining the on- or off-rates of the hybridization."

Appellant further argues on page 11 of the Brief that the cleaved probes would not or could not re-anneal.

Appellant's arguments are irrelevant because neither the claims nor the rejection requires any reannealing. The modification of the method of McGall with the teachings of Weng et al results in an array having at least two features wherein each feature comprises some probes that have been cleaved (i.e., depurination probes) and the remaining uncleaved probes (i.e., the nucleic acid ligands). The application of the second test condition (i.e., hybridization of the target nucleic acid analyte) results in binding of the target to the uncleaved ligands; thus, no reannealing of cleaved depurination probes is required.

Appellant also asserts on page 11 of the Brief that citations regarding depurination have been taken out of context and thus constitute cherry picking of phrases to cobble together the Appelants' invention.

Appellant's assertions are irrelevant since the basis for rejections of the claims is obviousness over the teachings of McGall in view of Weng et al rather anticipation. Thus, as noted above, the depurination steps and the hybridization to the target are interpreted as "test conditions," and the teachings of Weng et al render the claims obvious because Weng et al provide motivation for making the second test condition of McGall a hybridization to the target.

The examiner's interpretation of the teachings of the prior art of McGall therefore merely represents a total consideration of all of the teachings of McGall in accordance with the methodology of the ordinary artisan, wherein the sum total of the teachings of the work of another are considered as a whole by the ordinary artisan for the purpose of improving or optimizing a method of interest.

Thus, Appellant's assertion on page 11 of the Brief that McGall does not teach the claimed method is incorrect in view of the arguments presented above.

Appellant further argues on page 11 of the Brief that in the rejection of claims 1-13 in the Final Action of 22 December 2006, the examiner acknowledges that McGall does note explicitly teach hybridization as a test condition for depurination.

In contradistinction to claims 1-13, claims 21 and 23-25 do not required hybridization as a test condition for depurination. Independent claim 21 merely requires "detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample." While the array also has depurination probes, claims 21 and 23-25 do not require anything to bind to the depurination probe, nor is the binding used to determine the presence of depurination reaction products. Thus, the alleged deficiency of McGall with regard to independent claim 1 is moot with regard to independent claim 21 because the determination of depurination is not within the scope of claim 21.

Appellant also asserts on page 11 of the Brief that the specific embodiment of hybridization of a nucleic acid to the array followed by cleavage in not explicitly taught by McGall.

Appellant's assertions are irrelevant since the basis for rejections of the claims is obviousness over the teachings of McGall in view of Weng et al rather anticipation.. The hybridization to a target and the depurination are both interpreted as test conditions and Weng et al provides the motivation for using hybridization as one of the one or more test conditions taught by McGall.

Group VI: Claim 22

Appellant argues on pages 12-13 of the Brief that McGall fails to teach a sample including a collection of labeled target nucleic acid that specifically bind to the nucleic acid depurination features because McGall fails to teach hybridization to a labeled target nucleic acid.

Contrary to Appellant's argument, McGall clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. Appellant's assertion is therefore incorrect.

Appellant further argues on page 13 of the Brief that the cleaved probes would not or could not re-anneal.

Appellant's arguments are irrelevant because neither the claims nor the rejection requires any reannealing. The modification of the method of McGall with the teachings of Weng et al results in an array having at least two features wherein each feature comprises some probes that have been cleaved (i.e., depurination probes) and the remaining uncleaved probes (i.e., the nucleic acid ligands). The application of the second test condition (i.e., hybridization of the target nucleic acid analyte) results in binding of the target to the uncleaved ligands; thus, no reannealing of cleaved depurination probes is required.

Group I: Claims 1-7

Appellant asserts on pages 14-15 of the Brief that McGall does not teach contacting the substrate with a sample comprising a target nucleic acid.

Contrary to Appellant's assertion, McGall clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. Appellant's assertion is therefore incorrect.

Appellant further argues on pages 16-17 of the Brief that McGall does not teach hybridization to targets has an on- or off-rate.

Contrary to Appellant's argument, McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array is to obtain results of the assay by examining the on- or off-rates of the hybridization." Thus, Appellant is incorrect.

Appellant further argues on pages 16-17 of the Brief that the cleaved probes would not or could not re-anneal.

Appellant's arguments are irrelevant because neither the claims nor the rejection requires any reannealing. The modification of the method of McGall with the teachings of Weng et al results in an array having at least two features wherein each feature comprises some probes that have been cleaved (i.e., depurination probes) and the remaining uncleaved probes (i.e., the nucleic acid ligands). The application of the second test condition (i.e., hybridization of the target nucleic acid analyte) results in binding of the target to the uncleaved ligands; thus, no reannealing of cleaved depurination probes is required.

Appellant also asserts on pages 16-17 of the Brief that citations regarding depurination have been taken out of context and thus constitute cherry picking of phrases to cobble together the Appellant's invention.

Appellant's assertions are irrelevant since the basis for rejections of the claims is obviousness over the teachings of McGall in view of Weng et al rather anticipation. Thus, as noted above, the depurination steps and the hybridization to the target are interpreted as "test conditions," and the teachings of Weng et al render the claims obvious because Weng et al provide motivation for making the second test condition of McGall a hybridization to the target.

The examiner's interpretation of the teachings of the prior art of McGall therefore merely represents a total consideration of all of the teachings of McGall in accordance with the methodology of the ordinary artisan, wherein the sum total of the teachings of the work of another are considered as a whole by the ordinary artisan for the purpose of improving or optimizing a method of interest.

Thus, Appellant's assertion on page 17 of the Brief that McGall does not teach the claimed method is incorrect in view of the arguments presented above.

Appellant argues on page 18 of the Brief that even if McGall were modified to employ hybridization as a test condition, the combination would not detect the amount of binding complexes of depurination probes and target nucleic acids because McGall is not concerned with determining binding complexes.

Contrary to Appellant's argument, McGall clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. Appellant's assertion is therefore incorrect.

In addition, as noted above, lines 5-14 of page 16 of the instant specification states that "depurination probes are probes that have a known number of purine bases, and specifically Adenosine or A bases." Thus, the broadly claimed "depurination probe" encompasses any nucleic acid wherein the number of purine bases, regardless of whether or not any purine of the nucleic acid has been lost.

As also noted above, use of the hybridization test condition of Weng et al in the method of McGall is thus interpreted as outlined in the single exemplary embodiment: two ensembles of oligonucleotides in two areas of an array of McGall are both subjected to the same hybridization test condition of Weng et al (i.e., a first test condition). The ensemble in the first area is subjected to cleavage of depurination products (i.e., a second test condition). The amount of label at each site is detected and compared to determine the presence of depurination reaction products on the surface of the array. Thus, the resultant binding complexes of the uncleaved depurination probes with the target nucleic acid are compared to the cleaved binding complexes of the depurination probes with the target nucleic acid to determine the presence of depurination reaction products on the surface of the array.

Thus, in view of the arguments presented above, Appellant's arguments on page 18 of the Brief that hybridization as a test condition as taught by Weng et al does not remedy the alleged deficiencies of McGall is incorrect because the combination teaches detecting hybridization to all probes followed by detecting hybridization to only the uncleaved probes. The difference between the two assays determines the presence of depurination products because the second assay is missing the signals of the depurinated products that are present in the first assay.

Appellant asserts on page 19 of the Brief that the "probe" of McGall has no "target," and that, as a result, no features comprising depurination probes are contacted with a sample.

Contrary to Appellant's assertion, lines 5-14 of page 16 of the instant specification states that "depurination probes are probes that have a known number of purine bases, and specifically Adenosine or A bases." Thus, the broadly claimed "depurination probe" encompasses any nucleic acid wherein the number of purine bases, regardless of whether or not any purine of the nucleic acid has been lost. McGall

also clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate having a depurination probe with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. Appellant's assertion is therefore incorrect.

Appellant argues on page 19 of the Brief that "detection of depurination products" does not exhaust the limitations of the instant claims and that the detection of cleaved products which are no longer found on the features of the surface expressly fails to meet the limitations of the claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., detection of depurination products) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are directed to "detecting the amount of resultant binding complexes of said depurination probe and said target nucleic acid ins aid depurination feature to determine the presence of depurination reaction products on said surface." The claim does not require the direct detection of depurination products; rather, the claim merely required that the presence of depurination products is **determined**. The subtractive method of the prior art, wherein binding complexes are detected before and after cleavage, determines the presence of depurination products because the cleavage step reveals which probes are depurinated, and therefore meets the limitations of the claims.

Thus, in view of the arguments presented above, a prima facie case of obviousness has been established.

Group II: Claim 8

Appellant argues on page 20 of the Brief that the "probe" of McGall has no "target," and that, as a result, no features comprising depurination probes are contacted with a sample.

Contrary to Appellant's argument, lines 5-14 of page 16 of the instant specification states that "depurination probes are probes that have a known number of purine bases, and specifically Adenosine or A bases." Thus, the broadly claimed "depurination probe" encompasses any nucleic acid wherein the number of purine bases, regardless of whether or not any purine of the nucleic acid has been lost. McGall also clearly teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate having a depurination probe with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. Appellant's assertion is therefore incorrect.

Appellant also argues on pages 20-21 of the Brief that McGall fails to teach early or late probes whose synthesis is started at different increments of the in situ synthesis protocol as described on page 17, line 7-page 18, line 15 of the instant specification.

Appellant's arguments are irrelevant because the recitation cited by Appellant begins with the phrase "[i]n certain embodiments," thereby indicating that the description that follows is an exemplary embodiment but not necessarily a limiting definition. Thus, the probes of McGall are interpreted at least two ways. In the first embodiment, an "early depurination probe feature" is a feature comprising a probe with a depurinated position close to the substrate; i.e., early in the synthesis, as exemplified by the far right probe marked with a D in feature R2 of Figure 8. The "late depurination probe feature" is thus a feature comprising a probe with a depurinated position farther away from the substrate; i.e., late in the synthesis, as exemplified by the third probe from the left marked with a D in feature R2 of Figure 8. The

claim has therefore been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "early" and "late."

In a second exemplary embodiment, McGall teaches that the array is produced photolithographically (e.g., Figure 2), wherein each feature R1, R2, etc., comprises a plurality of different probes, wherein the synthesis of each of the different probes is started at a different time (last panel of Figure 2). Thus, McGall teaches at least a second embodiment of "early" and "late" depurination probes which is based on the position during the in situ synthesis protocol (i.e., photolithography) in accordance with the embodiment described on page 17, line 7-page 18, line 15 of the instant specification.

Group III: Claim 9

Appellant asserts on page 22 of the Brief that McGall does not teach two or more features having two or more identical depurination probe features having whose synthesis was started at different times.

Contrary to Appellant's assertion, McGall teaches an ensemble of sequence specific oligonucleotides is synthesized in an area (i.e., feature) R1 of the substrate, and an ensemble of oligonucleotides having the same (i.e., identical) sequence is synthesized in a second area (i.e., feature) R2 as well (column 9, lines 25-38), which is interpreted as having R2 synthesized subsequent to the synthesis of R1.

In addition, a review of the specification offers no guidance as to the amount of time between the synthesis of two areas that is considered "different times." Thus, even if reagents were added to features R1 and R2 at the same time, the different molecules of each feature do not all react simultaneously. Thus, at least some probes at one feature react at a different time as the probes of the other feature, and the synthesis of the features thus starts at different time.

Appellant also argues on pages 22-23 of the Brief that the probe and the target of McGall are the same molecule.

Contrary to Appellant's argument, McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)." Thus, McGall does in fact teach contacting the substrate having a depurination probe with a sample suspected of containing an analyte and detecting the presence of binding complexes on the surface of the array. Appellant's assertion is therefore incorrect because McGall teaches a probe on the array and a separate target.

Appellant further asserts on page 23 of the Brief that one of skill in the art understands that the claims as written refers to "early" or 'late" or "staggered start" probes, and that the ordinarily skilled artisan understands that the probes are distinguished by the cycle of the full-length synthesis during which their own synthesis commences.

Contrary to Appellant's assertion, the claim does not recite any of those terms. In addition, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Thus, the claims have been given the broadest reasonable interpretation consistent with the teachings of the specification regarding the teaching of "different times."

Group IV: Claim 13

Appellant argues on pages 23-25 of the Brief that McGall fails to teach the method of claim 12, in which the method is employed to evaluate the quality of a plurality of nucleic acid arrays because R1 and R2 are on a single substrate; i.e., a single array.

Contrary to Appellant's argument, claim 12 is **not** drawn to a method employed to evaluate the quality of a plurality of nucleic acid arrays, as stated at the bottom of page 24 of the Brief. Rather, it is claim 13 that is employed to evaluate the quality of a plurality of nucleic acid arrays.

It is noted that claim 1 is drawn to an "array that includes at least one depurination probe feature having a depurination probe." Lines 26-30 on page 7 of the instant specification asserts that a "substrate

may carry one, two, four or more arrays." Figure 8 of McGall shows a substrate having two features R1 and R2. Each area has an ensemble of sequence specific oligonucleotides, wherein, each ensemble comprises more that one distinct sequence, as exemplified by Figure 2. Thus, each ensemble is an array because each ensemble has a plurality of distinct sequences each in an area defined by the photolithographic synthesis.

Thus, the substrate of Figure 8 has two arrays. The first array comprises feature R1, which comprises an array in the form of an ensemble having a plurality of distinct sequences each in an area defined by the photolithographic synthesis. The second array comprises feature R2, which also comprises an array in the form of an ensemble having a plurality of distinct sequences each in an area defined by the photolithographic synthesis. The test conditions of McGall compare results of multiple areas R1, R2, etc (column 9, lines 20-67). Thus, the quality of a plurality of arrays is evaluated.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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